R E M A R K S

Information Disclosure Statement

On the copy of sheet 2 of the May 16, 2005 IDS Form returned with the July 29, 2008 Office Action, the Examiner drew a line through JP 2726672. However, JP 2726672 should have been considered and made of record, since it is a related family member of USP 4,952,581. The Examiner is therefore respectfully requested to return to the undersigned a copy of sheet 2 of the May 16, 2005 IDS Form, with the Examiner's initials next to each cited publication, including JP 2726672.

Specification Amendments

The brief description of the drawings was amended to correct minor clerical errors and to reply to the objection to the disclosure (which is discussed hereinbelow).

Claim Amendments

Claims 1 and 2 were amended to include the features of claims 3 and 4.

Claims 3, 4 and 13 to 16 were canceled.

The withdrawn claims 5 to 8, 17 to 20 and 22 were canceled. Applicants will shortly file a Divisional application, which includes the withdrawn claims 5 to 8, 12 to 20 and 22.

Rule 116

With respect of Rule 116, entry of the above claim amendments is respectfully requested, since such amendments involve features that were set forth in the claims prior to the final rejection.

Objection to the Disclosure

The disclosure was objected to for the reasons set forth in item no. 2 at the middle of page 2 of the Office Action.

The specification (the brief description of Figs. 3 and 4) was amended hereinabove to avoid the objection.

Withdrawal of the objection is therefore respectfully solicited.

Rejection Under 35 USC 112, First Paragraph

Claims 1 to 4, 13 to 16 and 21 were rejected under 35 USC 112, first paragraph, for the reasons set forth in item no. 4 at the bottom of page 3 of the Office Action.

This rejection concerned the terminology of "consisting essentially of" that was recited in claims 1 and 2.

Claims 1 and 2 were amended to revert to the previous terminology of "comprising."

Withdrawal of the 35 USC 112, first paragraph rejection is therefore respectfully requested.

Obviousness Rejections Under 35 USC 103

1. Claims 1 to 4 and 13 to 16 were rejected under 35 USC 103 as being unpatentable over EP 286903 ("Bito") in view of (i) USP 7,015,210 to Aiken, (ii) Rao et al., *Modulation of Aqueous Humor Outflow Facility by the Rho Kinase-Specific Inhibitor Y-27632*, 42, INV. OPHTHALMOL. VIS. SCI., 1029-1037, (April 2001) and (iii) USP 6,271,224 to Kapin et al. for the reasons set forth in item no. 5 on pages 4 to 6 of the January 12, 2009 Office Action.

It was admitted in the previous Office Action of July 29, 2008 that Bito, Aiken and Rao et al. describe different methods of treating glaucoma using prostaglandins and Rho inhibitors.

2. Claim 21 was rejected under 35 USC 103 as being unpatentable over EP 286903 ("Bito") in view of (i) USP 7,015,210 to Aiken, (ii) the Rao et al. publication and (iii) USP 6,271,224 to Kapin for the reasons stated in item no. 6 on pages 6 to 7 of the January 12, 2009 Office Action.

It was admitted in the January 12, 2009 Office Action that Bito, Aiken and Rao et al. describe different methods of treating glaucoma using prostaglandins and Rho inhibitors.

Rebuttal of the Obviousness Rejections

Bito et al. is directed to the use of a prostaglandin in combination with an adrenergic blocking agent for reduction of intraocular pressure (see the title of Bito et al.).

Aiken is directed to a method for treating or preventing ophthalmic disorders by reducing intraocular pressure

comprising the administration of one or more aldosterone receptor antagonists that contain a 9,11-epoxy moiety (see the Abstract of Aiken). As an optional further ingredient, Aiken mentions a prostaglandin (see claim 2 of Aiken).

Based on the discussion of Bito et al. in the last paragraph on page 4 of the Office Action and the discussion of Aiken in the first paragraph on page 5 of the Office Action, it is evident that Bito et al. and Aiken are being relied upon only for their disclosures of prostaglandins.

Clearly, Bito et al. and Aiken considered that the administration of a prostaglandin by itself was insufficient to effectively reduce intraocular pressure, so both Bito et al. and Aiken employed other drugs, namely an andrenergic blocking agent in Bito et al., and an aldosterone receptor antagonist containing a 9,11-epoxy moiety in Aiken. These other drugs employed by Bito et al. and Aiken are not recited in applicants' claims. Bito et al. and Aiken do not teach or suggest a Rho inhibitor as recited in applicants' present claims.

Rao et al. is directed to a Rho kinase-specific inhibitor Y-27632. Rao et al. do not teach or suggest combining such Rho kinase-specific inhibitor Y-27632 with a prostaglandin as recited in applicants' present claims.

Kapin et al. disclose a method of treating glaucoma by administering an isoquinolinesulfonyl compound (see the Abstract of Kapin et al.). Kapin et al. do not teach or suggest the specific combination of drugs as recited in applicants' present claims.

The obviousness rejections are based on the ground that it would have been obvious for one having ordinary skill in the art to combine and use two or three drugs having actions of reducing intraocular pressure, based on the four cited references. However, none of the four references disclose the specific combinations of compounds recited in applicants' present claims, nor describe the unexpected results achieved by the combination.

The Office Action neglects to address the serious potential difficulty when using plural drugs, namely, the possible serious drug-drug interactions. The combining of drugs is thus vastly different than the combining of non-drug chemical compounds, for example, detergents.

Thus, it is respectfully submitted that one of ordinary skill in the art would not consider to combine the references as set forth in the Office Action to attempt to arrive at the presently claimed invention. Moreover, assuming *arguendo* that the references were combinable, one having ordinary skill in the art would not arrive at the presently claimed invention by the combination of the four cited references.

As discussed hereinbelow, the presently claimed invention is further patentable based on the unexpected results set forth in the present specification.

The Examiner's attention is directed to the pharmacological test data in Fig. 2 of the present specification. Fig. 2 is reproduced as follows:

Fig. 2

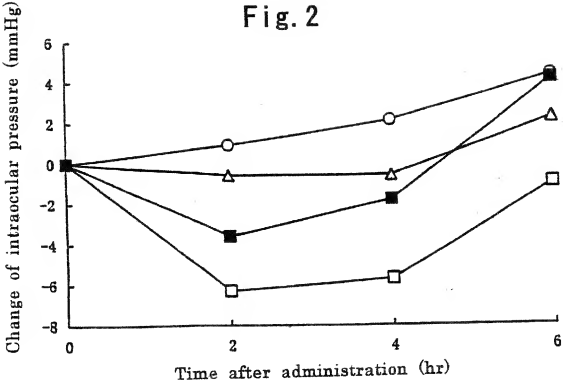
Change of intraocular pressure (mmHg)
6
4
2
0
-2
-4
-6
-8
0
2
4
6
Time after administration (hr)

Fig. 2 shows that intraocular pressure changes of a control group (○) and a group of Compound B (1-(5-isoquinolinesulfonyl)homopiperazine dihydrochloride) alone, (■) 6 hours after administration are almost the same. This indicates that the pharmacological effect of Compound B has been exhausted and no longer exhibits an intraocular pressure reducing effect. In other words, when Compound B and isopropyl unoprostone are administered in combination, if the effects are merely additive, the intraocular pressure reduction of the concurrently administered group (□) of Compound B and isopropyl unoprostone, 6 hours after administration should show the same value as that of isopropyl unoprostone alone (△). (The pharmacological effect of the group of Compound B (■) has been already exhausted). However, despite the pharmacological effect of the group of Compound B (■) being exhausted, the intraocular pressure reduction of the concurrently administered group (□) of Compound B and isopropyl unoprostone actually shows a much larger value (about 3 mmHg) than that of isopropyl unoprostone alone (△). In other words, Fig. 2 shows that

the concurrent administration of Compound B and isopropyl unoprostone (according to the presently claimed invention) brings about a synergistic result that would not be expected from the results of the compounds administered alone.

The same can be said for 8 hours after administration in Fig. 3 of the present application and 6 and/or 8 hours after administration in Fig. 4 of the present application. Fig. 3 is directed to the combined administration of latanoprost and Compound A ((R)-(+)-N-(1H-pyrrolo[2,3-b]pyridine-4-yl)-4-(1-aminoethyl)-benzamide dihydrochloride). Fig. 4 is directed to the combined administration of latanoprost and said Compound B.

As stated above, none of the four cited references disclose or suggest the specific combinations of compounds recited in applicants' present claims nor describe the unexpected results achieved by such combination. Thus, it is respectfully submitted that the presently claimed invention patentably distinguishes over the cited references, individually, or combined in the manner as set forth in the Office Action.

Withdrawal of each of the 35 USC 103 rejections is therefore respectfully requested.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,

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Encs.: (1) PETITION FOR EXTENSION OF TIME

(2) NOTICE OF APPEAL